REMARKS

Claims 1-30 are currently pending in the present application. Claims 1 and 25-30 are the only claims in independent form. The claims have been amended consistent with suggestions set forth in the Office Action and to correct minor typographical errors. In addition, the claims have been amended in order to remove non-elected subject matter as set forth in the Office Action. These amendments do not constitute new matter. Applicants reserve the right to file divisional applications pursuing the non-elected subject matter.

Specifically referring to the Office Action, claims 1-24 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for prodrugs of the compounds of formula (I). In response thereto and in order to expedite the allowance of the present application, the term "prodrugs" has been deleted from the claims. As a result, reconsideration of the rejection is respectfully requested.

Claims 1-24 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Number 6,011,155 to Villhauer (hereinafter, "the '155 patent.") According to the Office Action, the only difference between the presently claimed invention and the compounds disclosed in the '155 patent is that R1 of the present claims represents alkyl, while the '155 patent represents hydrogen. Therefore, according to the Office Action, it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results.

In response to the outstanding rejection, Applicants argue that the cited prior art neither discloses, suggests, or motivates to modify the cited prior art to provide for the claimed invention. More specifically, the prior art discloses various modifications at the 1 or 2-carbon position of the pyrrolidine ring, but the cite prior art references do not disclose or suggest the introduction of a substituent at the 5-carbon position of the pyrrolidine ring. In contrast, the presently claimed invention is directed towards substitutions at this position. As a result of these substitutions, different qualitative activities are provided by the presently claimed invention. In fact, the various compounds disclosed in the presently claimed invention demonstrate unexpected activity against human DPP-IV enzyme and/or rat DPP-IV enzyme. As set forth in the specification, the compounds of the present invention were found to inhibit DPP-IV induced fluorescence with inhibitory constants in a range of about 0.014 uM to about 7 uM. In addition,

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little was known about the effect of additional substitutions on the pyrrolidine ring. Thus, with the present invention, it was shown that substituents at the 5-carbon position of the pyrrolidine ring leads to compounds with superior selectivity profiles. Differences in potency were demonstrated between an unsubstituted 5-carbon and a substituted 5-carbon (e.g., methyl) on the pyrrolidine ring in the enclosed paper authored by the inventors (please see Table One of J.Med. Chem. 2006, 49, 6416-6420). Therefore, since the prior art neither discloses, suggests, nor motivates the modification of cited prior art and unexpected results exist with regard to the substitution of the 5-carbon position of the pyrrolidine ring. the obviousness rejection has been overcome. Reconsideration of the rejection is respectfully requested.

Claims 1-24 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of co-pending U.S. Patent Application Number 11/036.258 to Madar, et al. In response thereto and pursuant to 37 C.F.R. § 1.321, a terminal disclaimer is included herewith in order to overcome the rejection. Specifically, the terminal disclaimer identifies the patent application and term being disclaimed, states the present extent of the patentee's ownership interest, has been signed by an attorney of record, and is accompanied by the required fee. Additionally, a declaration is included herewith confirming that both pending applications are commonly owned. Reconsideration of the rejection is respectfully requested.

Claims 1-24 have been objected to as containing non-elected subject matter. In response thereto and in order to expedite the allowance of the present application, these claims have been amended to delete non-elected subject matter. Applicants reserve the right to file divisional applications to pursue the non-elected subject matter. Reconsideration of the objection is respectfully requested.
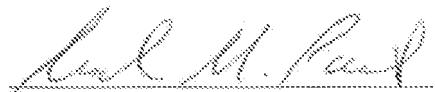
Claims 6, 10, 12, 16, 18, 20, 22, and 24 have also been rejected due to typographic errors of the last second compound of each of claim. According to the Office Action, the insertion of the term "and" would obviate the objection. In response thereto and pursuant to the suggestion set forth in the Office Action, the term "and" has been added to all of these claims. Reconsideration of the objection is respectfully requested.

In summary, the present amendment places the present application in condition for allowance, which allowance is respectfully requested. If any remaining issues exist, Applicants respectfully requests to be contacted through the undersigned below.

The Commissioner is hereby authorized to charge any additional Filing Fees required under 37 CFR §1.16, as well as any patent application processing fees under 37 CFR §1.17 associated with this communication for which full payment had not been tendered, to Deposit Account No. 01-0025.

Respectfully submitted,
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Discovery of 2-[4-{{2-(2S,5R)-2-Cyano-5-ethynyl-1-pyrrolidinyl]-2-oxoethyl]amino]-4-methyl-1-piperidinyl]-4-pyridinecarboxylic Acid (ABT-279): A Very Potent, Selective, Effective, and Well-Tolerated Inhibitor of Dipeptidyl Peptidase-IV, Useful for the Treatment of Diabetes

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Dipeptidyl peptidase-IV (DPP-IV) inhibitors are poised to be the next major drug class for the treatment of type 2 diabetes. Structure—activity studies of substitutions at the C5 position of the 2-cyanopyrrolidide warhead led to the discovery of potent inhibitors of DPP-IV that lack activity against DPP8 and DPP9. Further modification led to an extremely potent ($K_{iDPP-IV} = 1.0$ nM) and selective ($K_{iDPP8} > 30$ μM; $K_{iDPP9} > 30$ μM) clinical candidate, ABT-279, that is orally available, efficacious, and remarkably safe in preclinical safety studies.

Diabetes is a major health problem with over 150 million people diagnosed with type 2 diabetes worldwide.[1] It is estimated that only 12% of diagnosed type 2 diabetics in the U.S. achieve adequate glycemic control. Therefore, new therapies with novel mechanisms of action and improved tolerability are urgently needed to more effectively treat this disease. Glucagon-like peptide-1 (GLP-1) is a gut hormone released from L cells in the small intestine and proximal colon in response to the ingestion of nutrients and enhances the glucose-dependent secretion of insulin from pancreatic β-cells (incretin effect).[2] In type 2 diabetic patients, continuous infusion of GLP-1 decreases both fasted and postprandial blood glucose levels, improves β-cell function, and ultimately reduces hemoglobin A1c (HbA1c) concentrations.[3] Discontinuation of GLP-1 infusion in type 2 diabetics leads to the rapid reversion to hyperglycemia because GLP-1 activity is rapidly terminated by the action of the enzyme, dipeptidyl peptidase IV (DPP-IV), which cleaves the N-terminal dipeptide (His-Ala) of GLP-1.[4] Inhibition of DPP-IV activity is, therefore, a logical strategy to amplify the activity of endogenous GLP-1 and other incretins. DPP-IV inhibitors are clinically proven to effectively reduce HbA1c in diabetics and are expected to be the next major new class of oral antidiabetic agents.[5] GLP-1 infusion studies in uncontrolled diabetics have suggested that maximum glycemic control is achieved with 24 h infusion of GLP-1,[6] and our preclinical studies have further demonstrated that maximal glycemic control is achieved with >90% DPP-IV inhibition. In this context, we sought to identify DPP-IV inhibitors that possess a combination of potency and pharmacokinetic profile predicted to produce >90% DPP-IV inhibition for 24 h in man. Another criteria for DPP-IV inhibitor development are selectivity against the closely related enzymes, DPP8 and DPP9. Lack of
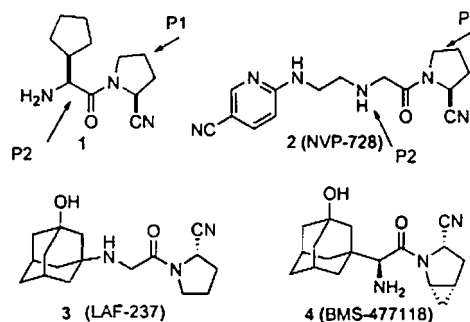

Figure 1. Cyanopyrrolidine DPP-IV inhibitors.

DPP8/DPP9 selectivity has recently emerged as a potential safety hurdle in the assessment of potential DPP-IV clinical candidates. Specifically, inhibitors of DPP8/DPP9 have been reported to cause profound toxicities in preclinical species.[7] Consequently, our objective was to identify DPP-IV inhibitors that have essentially no DPP8 or DPP9 inhibition at pharmacologically relevant exposures and have the potential to distinguish themselves from earlier clinical candidates in development. Herein we report the synthesis and pharmacologic profiles of a series of 5-alkynyl-2-cyanopyrrolidine compounds. These studies led to the discovery of 42 (ABT-279), a DPP-IV inhibitor with excellent potency ($K_{iDPP-IV} = 1.0$ nM) and selectivity ($K_{iDPP8} > 30$ μM; $K_{iDPP9} > 30$ μM, $K_{iDPP7} > 30$ μM, $K_{iPOP} > 30$ μM, $K_{iFAP-\alpha} > 30$ μM) that is orally available, efficacious, and exceptionally well-tolerated in preclinical safety pharmacology and toxicology studies.

Our initial medicinal chemistry efforts began with the 2-cyanopyrrolidines, illustrated by compounds 1 and 2, previously shown to be potent inhibitors of DPP-IV.[8] Recently, another two 2-cyanopyrrolidine compounds 3 and 4 have been disclosed that have advanced through Ph III clinical trials[9] (Figure 1). Compounds of this type interact with the enzyme by formation of an imidate with Ser 630 in the S1 pocket of the enzyme and interaction of the primary or secondary amine function of the P2 portion of the molecule with Glu 205/Glu

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Scheme 1[a]

5 → **6** → **7**

8 → **9** → **10**

11 → **12** → **13**
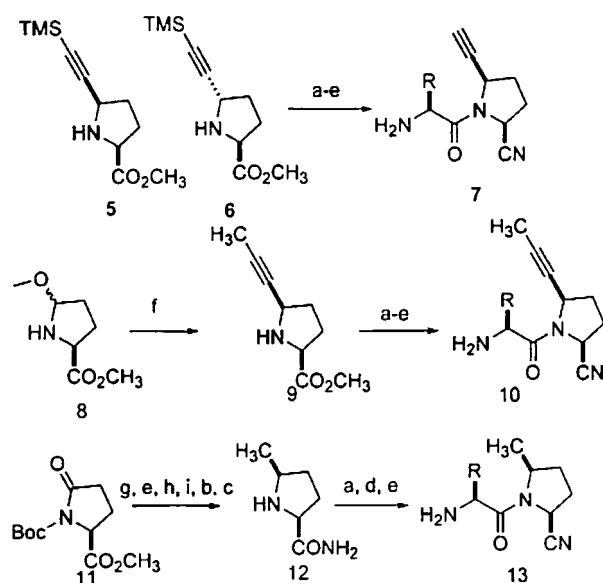
[a] Reagents: (a) N-Boc amino acid, EDAC, DMAP; (b) LiOH, THF; (c) isobutyl chloroformate, add NH_3 in dioxane; (d) $POCl_3$, imidazole, pyridine; (e) TFA, CH_2Cl_2 or HCl in ether; (f) trimethylsilylpropyne, $AlCl_3$, $SnCl_4 \cdot CH_2Cl_2$; (g) MeMgBr; (h) 50 psi H_2, cat. Pd/C; (i) Boc_2O, cat. DMAP.

Table 1. Substitutions on the C5 Position of 2-cyanopyrrolidine with a Primary Amine P2[a]

compd	R_1 (C5 Stereochemistry)	R_2	DPP-IV K_i(nM)
1	H	c-C_5H_9	1
14	≡—H (R)	i-Bu	8
15	CH₃ (R)	i-Bu	49
16	≡—H (R)	c-C_5H_9	8
17	CH₃ (R)	c-C_5H_9	97
18	CH=CH₂ (R)	c-C_5H_9	3,800
19	≡—CH₃ (R)	c-C_5H_5	24
20	≡—H (R)	c-C_6H_{11}	96
21	≡—H (S)	c-C_6H_{11}	>30,000
22	Ph (S)	sec-Bu	>30,000

[a] All K_i values are the average of at least two runs.

206. At the outset of our work, little was known about the effect of additional substitutions on the P1 pyrrolidine ring. However, we had anticipated that introduction of key substituents at position 4 or 5 of the pyrrolidine ring may lead to compounds with superior selectivity profiles when evaluated against closely related proteases. Ultimately, this premise proved to be correct.

Our initial thoughts on substitution were guided by homology models of DPP-IV based on the published structure of POP, which indicated only small substitutions at the C4 and C5 positions would be tolerated and substitution at C3 were precluded by the size of the S1 pocket. Systematic investigation of small substitutions at the C5 position of the pyrrolidine ring led to the discovery of 5-alkynyl-2-cyano pyrrolidines as potent DPP-IV inhibitors that have exquisite selectivity against the closely related enzymes DPP8 and DPP9.[10]

The synthesis of the dipeptides containing C5-substituted alkynyl pyrrolidines utilized chemistry described by Moeller et al. to prepare intermediates 5 and 6.[11] Standard peptide-coupling conditions were used to prepare the N-Boc-protected dipeptides. Installation of the nitrile function was accomplished by ester hydrolysis, preparation of the primary amide by a mixed anhydride protocol and dehydration with $POCl_3$ and imidazole in pyridine. The N-Boc group was either removed with TFA or HCl to provide inhibitor 7 (Scheme 1). To prepare the C5 propyne derivative, the previously described hemiaminal was treated with trimethylsilylpropyne and a mixture of aluminum trichloride and tin(IV) chloride. For preparation of the C5 methyl compound, N-Boc-protected pyroglutamic acid methyl ester 8 was treated with methylmagnesium bromide, the Boc group removed and reductive amination accomplished stereoselectively with hydrogen and palladium on carbon. The C5 ethylene compound 18 was prepared by partial reduction of the N-Boc-protected dipeptide with Lindlar's catalyst and subsequent removal of the Boc group with HCl.

All compounds were tested *in vitro* for DPP-IV inhibitory activity using affinity-purified human DPP-IV isolated from Caco-2 cells.[12] SAR comparison of the substitutions at the C5 position reveals that DPP-IV inhibitor potency is critically related to the size and stereochemistry of the C5 substituent.

The C5-unsubstituted compound 1 exhibited a potency of 1 nM (Table 1), while terminal alkyne substitution afforded an inhibitor 16 that was only slightly less potent. However, substitution of the larger methyl group 17 causes a significant decrease in DPP-IV inhibitory potency to 97 nM. Even more pronounced, the potency of the ethylene-substituted inhibitor 18 fell to nearly 4 μM. The propynyl substitution was tolerated, however, the analogue containing a phenyl group at C5 was found to be completely inactive. A comparison of inhibitors 20 and 21 illustrates the difference between R and S stereochemistry at the C5 position. Taken together, the SAR is consistent with a relatively small S1 pocket in the DPP-IV enzyme. Indeed, subsequent X-ray crystal structures of compounds 16 and 19 bound in the active site of the enzyme revealed that Tyr 548 is extremely close to the C5 position of the pyrrolidine ring thus restricting the size of tolerated substitutions (Figure 2).[13]

Although we were successful in identifying a substitution at the C5 position that maintained potency, compounds such as 16 did not have the required solution stability to warrant further evaluation.[14] We, therefore, began to investigate the effect of having an N-alkylglycine in the P2 portion of the inhibitor, knowing that inhibitors such as 2 had inherently better solution stability than those of type 1.

To synthesize the N-alkylglycine P2, C5-substituted P1 inhibitors, the previously prepared amines were acylated with chloroacetyl chloride, and the ester function was converted to the nitrile, as previously described. The α-chloroamides were then treated with a variety of primary amines (Scheme 2).

The *in vitro* potencies for a small selection of the compounds prepared are illustrated in Table 2. In general, only the terminal alkyne substituent at C5 allowed for N-alkyl glycine substituted P2 analogues that had potencies less than 100 nM. In comparing compound 28 with compounds 33 and 34, there was a significant loss in potency observed with the larger groups at C5. Of note, however, was the observation that analogues 31 and 32 had

Figure 2. X-ray structure of 42 in active site of DPP-IV (protein data bank code: 2I03).

Scheme 2[a]

R = -$\frac{\xi}{}$-C≡CH   23
-$\frac{\xi}{}$-C≡C-CH₃   24
—CH₃   25
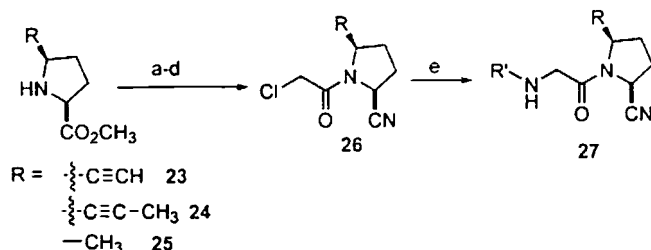
[a] Reagents: (a) chloroacetylchoride, Et₃N; (b) LiOH, THF; (c) isobutylchloroformate, NMM, add 0.5 M NH₃ in dioxane; (d) POCl₃, imidazole, pyridine; (e) R'NH₂, CH₃CN.

Table 2. N-Alkylglycine Substitution in P2 with C5 Substitution in P1[a]

compd	R₁	R₂	DPP-IV K_i(nM)
28	-ξ≡—H	c-C₅H₉	22
29	-ξ≡—H	c-C₆H₁₁	79
30	-ξ≡—H	HO⟨⟩·ξ	90
31	-ξ≡—H	NC⟨N⟩—O—⟨⟩ξ	5
32	-ξ≡—H	t-Bu	25
33	ξ-CH₃	c-C₅H₉	811
34	-ξ≡—CH₃	c-C₅H₉	959
35	-ξ≡—H	HO⟨⟩	62

[a] All K_i values are the average of at least two runs.

excellent inhibitory potencies against DPP-IV and had significantly longer solution stabilities than those compounds that contained a primary amine in P2. Compound 32, with the

Table 3. Selectivity of C5 Alkynl vs *des*-Alkynl Cyanopyrrolidines for DPP-IV vs DPP 8 and DPP9[a]

structure	compd	DPP-IV K_i(nM)	DPP8 K_i(nM)	DPP9 K_i(nM)
	1 R =H	1	4	3
	16 R = -ξ≡—H	8	17,700	>30,000
	37 R =H	4	110	10
	31 R = -ξ≡—H	5	>30,000	23,000
	3 R =H	4	1342	68
	35 R = -ξ≡—H	62	>30,000	>30,000
	38 R =H	10	12,360	3,300
	32 R = -ξ≡—H	25	>30,000	>30,000
	39 R =H	11	1,218	293
	28 R = -ξ≡—H	22	>30,000	>30,000

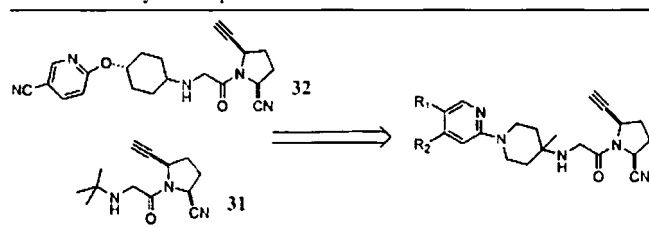[a] All K_i values are the average of at least two runs.

quaternary carbon α to the amine, was stable to heating at 37 °C in phosphate buffer for greater than 48 h.

We also examined the in vitro selectivity of the alkynyl-cyanopyrrolidines versus their *des*-C5-alkynyl counterparts. Table 3 illustrates the in vitro potencies against DPP-IV, DPP8, and DPP9.[15] In all cases examined, there was a dramatic improvement in inhibitor selectivity against DPP8 and DPP9 due to introduction of the alkyne group at C5 of the P1 cyanopyrrolidine ring. This magnitude of DPP8/9 selectivity was not observed with other C5/C4 substituents on the cyanopyrrolidine ring such as the C5/C4 cyclopropyl modification in compound 4 ($K_{iDPP-IV}$ = 0.6 nM; K_{iDPP8} = 130 ± 12 nM, K_{iDPP9} = 71 ± 4 nM).

To further optimize the potency of this series, we chose to focus on merging the chemical stability seen with analogues such as 32 with the high potency seen with more extended analogues such as 31. To eliminate the need for a chiral center, we focused on substituted piperidine analogues such as compound 40 that had good, but not optimal, potency in our DPP-IV assay. Examination of compounds related to 40 bound in the active site of DPP-IV revealed that Arg 125 and His126 would be in close proximity to the pyridine ring of 40 and postulated that proper substitution with a carboxylate residue on the pyridine ring would impart enhanced binding through a salt bridge between the acid and the protonated form of the histidine. Gratifyingly, compounds 41 and 42 gave enhanced potencies of approximately 1 nM while retaining exquisite selectivity against DPP8, DPP9, DPP7, prolyloligo peptidase (POP) and fibroblast activating protein-α (FAP-α; Table 4).[16,17]

Indeed, an X-ray crystal structure of 42 bound in the active site of human DPP-IV revealed several critical interactions necessary for potent inhibition (Figure 2). Specifically, the pyridine moiety of 42 stacks with Arg 125 of DPP-IV, and His126 forms a salt bridge to the carboxylate of 42. Another interesting feature of the X-ray structure was the narrow tunnel

Table 4. *N*-Arylated Piperidine DPP-IV Inhibitors

(structures 32, 31)

	DPP-IV K_i (nM)	DPP 8 K_i (nM)	DPP 9 K_i (nM)	DPP 7 K_i (nM)	POP K_i (nM)	FAP-α K_i (nM)
40 R1 = −CN R2 = H	3	>30 000	>30 000	>30 000	>30 000	>30 000
41 R1 = −CO$_2$H R2 = H	1.3	>30 000	>30 000	>30 000	>30 000	>30 000
42 ABT-279 R$_1$ = H R$_2$ = CO$_2$H	1.0	>30 000	>30 000	>30 000	>30 000	>30 000

ᵃ All K_i values are the average of at least two runs.

Table 5. Selected PK Parameters for 42ᵃ

	Intravenous Dose				
species (dose)	$T_{1/2}$ (hr)	V_{ss} (L/kg)	V_β (L/Kg)	AUC (μg-hr/mL)	CLp (L/hr-kg)
rat (5 mg/kg)	6.8	2.2	6.7	7.6	0.68
monkey (2.5 mg/kg)	1.7	0.3	1.3	5.2	0.51
dog (2.5 mg/kg)	6.4	1.5	8.5	2.8	0.91

	Oral Dose			
species (dose)	$T_{1/2}$ (hr)	C_{max} (μg/mL)	T_{max} (hr)	AUC (μg-hr/mL)	F (%)
rat (5 mg/kg)	4.7	0.37	4.7	2.1	28.0
monkey (2.5 mg/kg)	2.0	0.14	2.7	0.58	11.2
dog (2.5 mg/kg)	5.3	0.3	0.8	0.97	35.2

ᵃ V_{ss} is the volume at steady-state concentration, V_β is the volume of the beta phase, AUC is the area under the curve, CLp is the plasma clearance, C_{max} is the maximal concentration, T_{max} is the time at maximal concentration, and F is the oral bioavailability. The PK values are averages of at least six rats.

formed by Tyr547 and Phe357 of DPP-IV that accommodates the ethynyl group of 42.

The pharmacokinetics of 42 were subsequently investigated in the Sprague−Dawley rat, beagle dog, and cynomolgous monkey (Table 5). Compound 42 was characterized by moderate clearance across species with oral half-lives of 2 (monkey) to 5.3 h (dogs).

Compound 42 was efficacious in a Zucker diabetic fatty (ZDF) rat model of impaired glucose tolerance[18] (Figure 3). Briefly, 10-week old female ZDF rats were differentially dosed with either vehicle or 42 after an overnight fast. Four hours later (t = 0), the rats were allowed 4-hour free access to a highly palatable, macronutrient balanced food source (Ensure). This model is analogous to an oral glucose tolerance test (OGTT) used clinically to evaluate glycemic control, except that the "challenge" is a liquid mixed meal. At 4 h post-dose, 42 (1 mg/kg) produced plasma drug levels of 18 ng/mL and caused an 87% inhibition of plasma DPP-IV activity (data not shown). This level of DPP-IV inhibition resulted in a 4-fold increase in circulating active GLP-1 levels (t = 10 min: 42 vs vehicle; 29 pM vs 7 pM) leading to a 60% increase in insulin (t = 10 min: 42 vs vehicle; 39 ng/mL vs 24 ng/mL) and a 50% reduction in glucagon levels (t = 30 min: 42 vs vehicle; 42 pg/dL vs 93
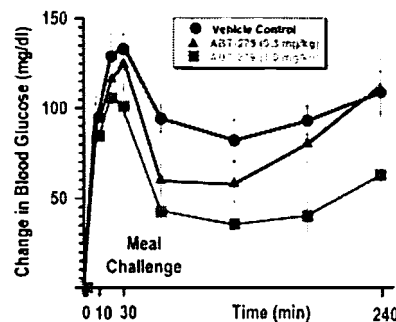

Figure 3. Compound 42 improves glucose tolerance in the female ZDF rat. Compound 42 was orally dosed 4 h prior to the rats being allowed to free feed for 4 h on a mixed meal. Data are expressed as mean ± SEM (n = 10/group).

pg/dL), culminating in a 50% reduction in postprandial glucose excursion (AUC$_{glucose\ (0-240\ min)}$: 42 vs vehicle; 12 470 mg/dL·min vs 22 860 mg/dL·min; Figure 3).

Compound 42 exhibited an excellent preclinical safety profile. It showed no inhibition of major liver metabolic enzymes such as CYP3A4, CYP2D6, and CYP2C9 (IC$_{50}$ > 30 μM). Compound 42 lacked detectable binding to the hERG channel (K_i > 45.1 μM) and showed a remarkably benign hemodynamic and electrocardiographic profile when administered intravenously to either anesthetized rats or dogs at concentrations up to 28 μg/mL; that is, 900× the effective plasma concentration (30 ng/mL) determined in efficacy studies. It is negative in the miniAmes mutagenicity test up to 2 mg/well and negative in murine *in vivo* clastogenicity test at concentrations up to 2000 mg/kg. In 4-week studies in rats and dogs, the "no observed adverse effect level" was greater than 1000 mg/kg/day (rat AUC$_{0-24h}$ = 39 μg·hr/mL; dog AUC$_{0-24h}$ = 36 μg·hr/mL). Based on its combined profile of excellent potency, selectivity, efficacy, and *in vivo* safety, 42 was selected as a candidate for clinical evaluation in humans.

Experimental Section

The synthesis of compound 42 is indicated below (the last two steps). For more information (procedures for all intermediates and final compounds), see Supporting Information.

(2S,5R)-5-Ethynyl-1-{N-(4-methyl-1-(4-carboxy-pyridin-2-yl)-piperidin-4-yl)glycyl}pyrrolidine-2-carbonitrile (42). To a stirred solution of (2S,5R)-1-(chloroacetyl)-5-ethynylpyrrolidine-2-carbonitrile (0.058 g, 0.30 mmol) in dioxane (3.0 mL) and water (1.0 mL) at room temperature was added 4-amino-4-methyl-3,4,5,6-tetrahydro-2H-(1,2′)bipyridinyl-4′-carboxylic acid *tert*-butyl ester (0.170 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 48 h, concentrated under reduced pressure and purified by flash chromatography with 5% methanol in dichloromethane. The product was mixed with TFA in dichloromethane (1:1, 6 mL), and after 2 h, the volatiles were removed under reduced pressure. The residue was triturated with diethyl ether to provide the titled compound as the TFA salt. MS (CI) *m/z* 396 (M + 1)⁺; ¹H NMR (300 MHz, methanol-d_4) δ ppm 8.17 (d, 1H), 7.67 (s,-1H), 7.31 (dd, 1H), 4.84 (m, 2H), 4.34−4.15 (m, 4H), 3.41−3.35 (m, 2H), 3.20 (m, 1H), 2.52−2.24 (m, 5H), 2.07−2.00 (m, 4H), 1.59 (s, 3H). Anal. (C$_{21}$H$_{25}$N$_5$O$_3$·2.3 TFA) C, H, N.

Supporting Information Available: Experimental procedures including characterization data for new compounds and biological experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The K_i for rat DPP-IV is 1.0 nM.